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DRINKER BIDDLE & REATH
ATTN: INTELLECTUAL PROPERTY GROUP
ONE LOGAN SQUARE
18TH AND CHERRY STREETS
PHILADELPHIA, PA 19103-6996

EXAMINER	
GHALI, ISIS A D	

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1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/621,711	CHIEN, TE-YEN	
	Examiner	Art Unit	
	Isis A. Ghali	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *163-182* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *163-182* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The receipt is acknowledged of applicant's amendment and a copy of the previously filed declaration, both filed 10/31/2007.

Claims 163-180 have been previously presented, and claims 181 and 182 have been added.

Claims 163-182 are pending and included in the prosecution.

The following rejection has been overcome by virtue of applicants' amendment and remarks:

The rejection of claims 163-175, and 177-180 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement by introducing new matter.

The following rejections have been discussed in details in the previous office action, and are maintained for reasons of record:

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 176 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 176 to recite "more than 10% and less than 30%" that is not described in the specification. In paragraph 0065 applicants disclosed that the total amount of enhancer mixture in the dried adhesive polymer matrix is about 12-36% w/w of the polymer matrix. Therefore, no disclosure of amount between about 10 and 30% as instantly claimed. In paragraph 54, applicants disclosed between about 10 and about 30 percent of skin permeation enhancer combination based on the weight of the adhesive polymer **starting solution**, and not the adhesive matrix in the final claimed product.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 163-182 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 7,045,145. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed subject mater is fully claimed and covered by the claims of the issued patent 7,045,145. The present claims and the claims in the issued patent are directed to common subject matter as follows: a transdermal delivery system comprising backing layer and adhesive polymer matrix layer affixed to the backing layer, wherein the adhesive polymer matrix comprising an adhesive polymer, a humectant, an estrogen, a progestin, and a combination of permeation enhancers comprising dimethyl sulfoxide, a fatty acid (C_8-C_{20}) alcohol ester of lactic acid, a lower (C_1-C_4) alkyl ester of lactic acid, and capric acid. The adhesive matrix is polyacrylate copolymer of 2-ethylhexyl acrylate and vinyl acetate and the humectant is polyvinyl pyrrolidone copolymer with vinyl acetate. The estrogen is 17-β-estradiol and progestin is levonorgestrel.

The examiner acknowledges applicants' intent to hold filling terminal disclaimer till determination of allowable subject matter.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 163-166 and 171-182 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,762,956 of ('956) in view US 5,023,084 ('084).

US '956 teaches a transdermal contraceptive delivery system comprising impermeable backing layer and adhesive matrix comprising combination of 17-β-estradiol and levonorgestrel, copolymer of 2-ethylhexyl acrylate and 3-60% of vinyl acetate, humectant, and combination of permeation enhancers comprising dimethyl sulfoxide, lauryl lactate and ethyl lactate (abstract; col.5, lines 37-60; col.6, lines 5-6, 47-48col.7, lines 50-60; col.9, lines 5-10col.16, lines 47-67). US '956 teaches amount of enhancer combination amount up to 30-60% of the matrix (col.3, lines 39-40), and this amount encompasses the claimed amount that can be less than 30%.

US '956 does not teach the capric acid in the mixture of permeation enhancers.

US '084 teaches transdermal estrogen/progesterone absorption dosage unit comprising adhesive matrix comprising permeation enhancers. US '084 teaches capric acid as the preferred enhancing agent because it provides highly satisfactory skin absorption enhancement, (abstract; col.17, lines 25-57). US '084 teaches capric acid in

amount as low as 10% (col.17, lines 50-52), and teaches high amounts interferes with adhesive properties and its satisfactory adhesion to the skin (col.17, lines 55-58).

Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide transdermal delivery device to deliver combination of estrogen and progesterone in an adhesive polymer matrix comprising combination of enhancers comprising dimethyl sulfoxide, lauryl lactate and ethyl lactate as disclosed by US '956, and further add capric acid to the adhesive combination as disclosed by US '084, motivated by the teaching of US '084 that capric acid is a preferred enhancer for estrogen and progesterone combination because it provides highly satisfactory skin absorption enhancement, with reasonable expectation of having a transdermal delivery device comprises adhesive polymer matrix comprising a combination of dimethyl sulfoxide, lauryl lactate, ethyl lactate and capric acid with highly satisfactory skin absorption enhancement for the combination of estrogen and progesterone. Regarding the amount of the enhancer combination, US '956 suggests amounts up to 30%-60%, as instantly claimed, and one having ordinary skill in the art intended to further add another enhancer to the combination of US '956, is expected to reduce the amount of each component of the enhancer combination in order to replace percentage of the combination of enhancer with a new member, and further one having ordinary skill in the art would have added as low as 10% of capric acid because US '984 teaches that higher amounts interferes with adhesive satisfaction.

7. Claims 167-170 are rejected under 35 U.S.C. 103(a) as being unpatentable over US '956 in view of US '084 as applied to claims 163-166 and 171-174 above, and further in view of US 6,007,835 ('835).

The teachings of US '956 and US '084 are discussed above.

However, the combination of the references does not teach polyvinyl pyrrolidone (PVP) or PVP copolymer with vinyl acetate (VA) as claimed in claims 167-170.

US '835 teaches transdermal delivery system for steroid hormones comprising and adhesive matrix comprising PVP/VA-S-630 that has content of 40% 0f VA and 60% PVP (abstract; col.4, lines 33-39). PVP/VA copolymer provides a matrix that exhibits the desired ergonomic and therapeutic properties, and makes it possible to obtain remarkable yield (col.6, lines 12-16). PVP/VA copolymer enhances the solubility of the hormones, and surprisingly, makes it possible to enhance the adhesion of the matrix to the skin and also causes reduction in skin irritation (col.6, lines 35-41).

Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide transdermal delivery device to deliver combination of estrogen and progesterone in an adhesive polymer matrix comprising humectant and combination of enhancers comprising dimethyl sulfoxide, lauryl lactate, ethyl lactate and capric acid as disclosed by the combined teachings of US '956 and US '084, and replace the humectant by PVP/VA-S-630 copolymer disclosed by US '835, motivated by the teaching of US '835 that PVP/VA copolymer provides a matrix that exhibits the desired ergonomic properties with remarkable yield, enhances the solubility of the hormones, and surprisingly, makes it possible to enhance the adhesion of the matrix to

the skin and also causes reduction in skin irritation, with reasonable expectation of having adhesive polymer matrix to deliver combination of hormones comprising combination of enhancers and PVP/VA-S-630 copolymer wherein the matrix exhibits the desired ergonomic properties with remarkable yield, enhances the solubility of the hormones, enhances the adhesion of the matrix to the skin and also causes reduction in skin irritation.

Response to Arguments

8. Applicant's arguments filed 10/31/2007 have been fully considered but they are not persuasive.

Applicants traverse the obviousness rejection of claims163-166 and 171-174 over US '956 in view '084 and the obviousness rejection of claims 167-170 further in view '835 by arguing that:

- US '956 teaches only the combination of three enhancers and does not show the desirability of adding a fourth enhancer, and use the terms as "consisting of" and "unique combination". US '084 does not teaches the use of capric acid in combination with other enhancers and teaches as low as 10% capric acid with preferred amount 15-30% while the present claims recites between 3-9%. Therefore, no motivation to combine the references.

In response to these applicant's arguments, applicants' attention is drawn to the scope of the present claims 163-166 and 171-174 that are directed to composition, and all the elements of the composition are disclosed by the combined teaching of US '956 and US '084. US '956 teaches every element of the present invention except for one

component of the enhancer, and this missing component is taught by US '084. US '956 teaches total enhancer between 35-36%, which overlaps with the present disclosure 12-36%. US '084 teaches, unlike applicants' assertion, the use of combination of two or more enhancers that frequently provides superior results such as greater absorption of steroid hormones, col.17, lines 20-24. Also US '084 teaches that capric acid is a preferred enhancing agent for steroid hormones, col.17, lines 45-46. Therefore the art recognized the combination of enhancers and also recognized capric acid as a preferred enhancer for the steroid hormones, and this would have motivated one having ordinary skill in the art to add capric acid to the combination of enhancers disclosed by US '956. It is obvious to one having ordinary skill in the art to reduce the amount of capric acid less than 10% attempting to add capric acid to the combination of the enhancers disclosed by US '956. The disclosed examples and preferred embodiment do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971).

Additionally, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). US '956 and US '084 show that it was well known in the art at the time of the invention to use the claimed ingredients in a composition to enhance the transdermal delivery of steroid hormones. It is a *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same

purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten,* 459 F.2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi*, 58 CCPA 1074, 1079-80) 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960).

Based on the disclosure by US '956 and US '084 references that the claimed substances are used in transdermal devices as permeation enhancer for steroid hormones, an artisan of ordinary skill would have a reasonable expectation that a combination of the substances would also be useful in creating compositions to enhance transdermal delivery of steroid hormones. Therefore, the artisan would have been motivated to combine the claimed enhancers into a single composition. No patentable invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients. See *In re Sussman*, 1943 C.D. 518; *In re Huellmantel* 139 USPQ 496; *In re Crockett* 126 USPQ 186.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide

transdermal delivery device to deliver combined estrogen and progesterone in a matrix comprising combination of enhancers as disclosed by US '956, and add capric acid to the matrix as disclosed by US '084, motivated by the teaching of US '084 that the combination of enhancers containing capric acid provides highly satisfactory skin absorption enhancement and satisfactory adhesion and also motivated by the teaching of US '084 that capric acid is a preferred enhancer for steroid sex hormones when combination with other enhancers, with reasonable expectation of having a transdermal delivery device that comprises a combination of permeation enhancers in its matrix containing dimethyl sulfoxide, lauryl lactate, ethyl lactate and capric acid that deliver steroidal hormonal combination to the skin of the user at a satisfactory enhanced rate.

It is well established that a conclusion of obviousness under 35 U.S.C. 103 (a) does not require absolute predictability, only a reasonable expectation of success; and references are evaluated by what they suggest to one versed in the art, rather than by their specific disclosure. *In re Bozek*, 163 USPQ 545 (CCPA 1969). In considering the disclosure of the reference, it is proper to take into account not only the specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom. *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968). The rational to modify or to combine the prior art does not have to be expressly stated in the prior art; the rational may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art. It is not necessary that the prior art suggest the

combination or modification to achieve the same advantage or result discovered by applicant. *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972).

- Applicants argue that the addition of US '835 to support rejection of claims 167-170 is untenable in view of absence of teaching in US '956 and US '084 and does not supply suggestion to combine the cited references for teachings absent from the primary references.

Regarding this argument, it is argued that US '835 is relied upon for the solely teaching of the specific humectants in the transdermal matrices and to show that such humectants are known in the transdermal art. Further, US '835 teaches PVP/VA-S-630 copolymer provides a matrix that exhibits the desired ergonomic properties with remarkable yield, enhances the solubility of the hormones, and surprisingly, makes it possible to enhance the adhesion of the matrix to the skin and also causes reduction in skin irritation. This teaching would have motivated one having ordinary skill in the art at the time of the invention to include PVP/VA in transdermal matrices with reasonable expectation of having adhesive polymer comprising PVP/VA-S-630 copolymer wherein the matrix exhibits the desired ergonomic properties with remarkable yield, enhances the solubility of the hormones, enhances the adhesion of the matrix to the skin and also causes reduction in skin irritation.

- Applicants argue that the declarations filed 11/09/2006 provides rebuttal evidence of no-obviousness. The declaration of Dr. Kydonieus shows that when chemical enhancers are employed, the complexity and unpredictability of transdermal systems increases because they behave substantially differently when co-delivered with other enhancers and with the drugs themselves. For these reasons, the effect of enhancers on the skin permeation of drugs is

> unpredictable and dependent on many variables whose effect can only be determined by experimentation. Dr. Kydonieus points out that the system of the 956 patent was deficient in part because of insufficient delivery of progestin hormone to the bloodstream, and the 084 patent's information was completely insufficient to provide the skilled artisan with any guidance as to how to improve on the system of the 956 patent in the manner claimed in the present application. The Declaration of Dr. Kydonieus provides comparative in vitro and in vivo data presented by the 956 patent and the present application and its parent and points out that the in vitro skin flux results with the capric-acid containing patch of the present invention were actually poorer than that of the 956 patent's transdermal system, yet in the clinical studies, the steady state serum concentration of progestin delivered by the present invention's system was several-fold better than that delivered by the same size patch of the 956 patent's system. Dr. Kydonieus is of the opinion that this many- fold improvement in vivo progestin delivery by re-formulating the matrix to include a small amount of capric acid was not expected, and could not have been predicted from the information presented in the 956 patent or the 084 patent. The declaration shows commercial success of the product as claimed.

In response to this argument, it is noticed that comparative date does not commensurate in scope of the present invention. The data does not show superior and unexpected results of the present claims over the combined teaching of US '956 that disclosed combination of the three enhancers: dimethyl sulfoxide, lauryl lactate, ethyl lactate, and US '084 that teaches capric acid. Furthermore the table at page 9 of the declaration shows the effect of 43% of total combined enhancer while the present invention disclosed only 12-36% total combined enhancer. Additionally, the table compares figures of the parent application that disclosed higher amount of the total enhancer combination, and the present application does not contain figures at all. Regarding the comparison example 2 of the parent of the present invention with example 2 of US '956, it is noticed that the scope of the claims is broad covering any amounts and ratios of the first three claimed enhancers while the declaration is limited

to specific amount of each ingredient according to example 2 of the parent application. The single and specific amount of each enhancer in the composition of the declaration does not support the generic concept of the claims. Regarding the declaration of Thomas Rossi: The declaration shows commercial success of the product as claimed. However, it is established that the commercial success does not support non-obviousness.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis A. Ghali whose telephone number is (571) 272-

0595. The examiner can normally be reached on Monday-Thursday, 6:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Isis A Ghali
Primary Examiner
Art Unit 1611

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ISIS GHALI
PRIMARY EXAMINER